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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/647,678	12/08/2000	Gerardo Byk	ST98009	9996

5487 7590 03/10/2004

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/647,678	BYK ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-18 and 22-28* is/are rejected.

7)☐ Claim(s) *19-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/5/01, 1/20/04,,*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information disclosure statements were received on 7/5/01, 1/20/04, and 1/23/04.

Applicants response to restriction requirement was received and entered on 12/15/03. Applicant elected with traverse group 2, claims 1-23 drawn to compounds of general structure CA-Rep-R, wherein R is lipidic and R1 is hydrophilic. After further consideration the restriction requirement is withdrawn. The full breadth of the claims was searched to the extent possible given their indefiniteness.

Claims 1-28 remain pending in the application. Claims 19-21 were not considered in this Office Action because they are improper multiple dependent claims (see below under claim objections).

Drawings

Applicant has submitted drawings which are adequate for the purpose of examination.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired (i.e. 60/085,845, and PCT /FR99/00740) must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional

application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Receipt is acknowledged of a certified copy of the foreign application referred to in the oath or declaration or in an application data sheet. If this copy is being filed to obtain the benefits of the foreign filing date under 35 U.S.C. 119(a)-(d), applicant should also file a claim for such priority as required by 35 U.S.C. 119(b). If the application being examined is an original application filed under 35 U.S.C. 111(a) (other than a design application) on or after November 29, 2000, the claim for priority must be presented during the pendency of the application, and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior foreign application. See 37 CFR 1.55(a)(1)(i). If the application being examined has entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the claim for priority must be made during the pendency of the application and within the time limit set forth in the PCT and Regulations of the PCT. See 37 CFR 1.55(a)(1)(ii). Any claim for priority under 35 U.S.C. 119(a)-(d) or (f) or 365(a) or (b) not presented within the time period set forth in 37 CFR 1.55(a)(1) is considered to have been waived. If a claim for foreign priority is presented after the time period set forth in 37 CFR 1.55(a)(1), the claim may be accepted if the claim properly identifies the prior foreign application and is accompanied by a grantable petition to accept an unintentionally delayed claim for priority. See 37 CFR 1.55(c).

Claim Objections

Claim 1 is objected to for the following reasons:

At page 80, line 5, the word "bond" should be substituted for the word "bonding" because an object ("R_2") is specified, and not an action. Alternatively the words "site for" could be inserted directly after "bonding". A similar situation exists at page 80, lines 12 and 18.

At page 80, line 7 'The' should not be capitalized.

At page 80, lines 8 and 14, and page 82, lines 10, 17, and 18, asterisks should be deleted and replaced by bullets, or some other character, because asterisks were defined in the claim at page 79, lines 20-22 as 14 as a hydrogen atom or a bonding site.

Claim 8 is objected to because "chotestanyl" at line 19 is misspelled.

Claims 10 and 11 are objected to because they are incomplete sentences inasmuch as they lack an article modifying the noun "Method". Insertion of "A" is suggested. Claims 12 is objected to for similar reasons.

Claim 18 is objected to because it lacks a comma after "histone".

Claims 19-21 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Claims 19-21 depend from claims 12-19, of which claim 14 is a multiple dependent claim. Accordingly, claims 19-21 have not been further treated on the merits.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 24 and 25 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Although claims 12, 26, and 28 are independent claims, they require a "compound of general formula I", which is defined in claim 1. As a result many of the indefiniteness rejections that apply to claim 1, also apply to claim 12, 26, and 28, and their dependents.

Claims 1-25, and 29 are indefinite because they are drawn to a compound in a "DL form". To the Examiner's knowledge this is not possible. A pure solution of a compound either rotates plane polarized light to the right (D), or to the left (L). A single compound cannot in the end do both. Generally the term DL (or D,L) is used to refer to racemic mixtures of D compounds and L compounds.

Claims 1-8, 10-25, and 29 are indefinite because they recite "the different groups $[CH_2)_p$-Y]" without proper antecedent basis. This phrase implies that there must be different groups $[CH_2)_p$-Y]. However, according to the claims, as few as 0 or 1 groups $[CH_2)_p$-Y] are allowed, so there need not be different groups $[CH_2)_p$-Y] . A similar situation arises at page 81, lines 7- 8, lines 9-10, and lines 16-17 with respect to "the different groups $-NR_4$-$(CH)_r$-, and "the different groups $-NR_4$-$(CH)_rR_{3''}$, and "the different groups $-(CH_2)_s$-NR_5".

Claims 1-8, 10-25, and 29 are indefinite because it is unclear what are the metes and bounds of 'Y'. The claim limits 'Y' to one of carbonyl, amino, methylamino, and methylene, but then indicates that it may have "different meanings within the different groups". This phrase could mean that 'Y' is limited to one of the indicated identities, or that 'Y' could have some other undisclosed identity. As such, the metes and bounds of the term 'Y' are unclear.

Similarly the metes and bounds of 'r' are unclear as defined at page 81, lines 6-8, because the claim limits 'r' on the one hand to be between 0 and 10 inclusive, but subsequently allows 'r' to have "different meanings". A similar

situation exists for the term 's' at page 81, lines 14-16, the term "CA" at page 81 lines 18 and 19 and page 82, lines 4-6, for general formula VII at page 82, lines 1 and 2.

Claims 1-8, 10-25, and 29 are indefinite because they lack proper antecedent basis for the phrase "whose nitrogen atom" at page 81, line 2 in the description of formula VI. Formula VI allows for up to 8 nitrogen atoms. Insertion of the word "terminal" immediately before "nitrogen" is suggested.

Claims 1-8, 10-25, and 29 are indefinite because the phrase "depending on the cases" is confusing. The only antecedent for "the cases" is recitation of "1st case" and "2nd case", but the claim does not clearly indicate that these are what is referred to, and the nature of the recited dependency is unclear. It is suggested that the claim should read "whose terminal nitrogen atom is attached to one of atoms X, V, W, or Z of general formula II when the compound comprises general structural formula IV, or to the substituent Y of the group R_1 when the compound comprises general structural formula V.

Claims 1-8, 10-25, and 29 is indefinite because the metes and bounds of "steroid derivative" are unclear. Neither the specification nor the claim defines the term, so one of skill in the art cannot know the metes and bounds of the claim.

Claims 1-8, 10-25, and 29 is indefinite because it is unclear what is intended by formula VII. Formula VII is described at page 81, line 13 to page 84, line 2. The indefiniteness arises because variable group R5, which is attached to

formula VII may itself be a group of general formula VII. This results in an infinitely circular definition that has no meaning. For example, if one wished to add to formula VII a group R5 which is also formula VII, the definition of formula VII would necessarily change, and one would not have added a group R5 that is formula VII. In fact, one cannot, so the claim is indefinite.

Claims 1-8, 10-25, and 29 are indefinite because R' is defined at page 82, lines 10-15 as representing either a group of formula NHR_6R_7, for which R_6 and R_7 may independently represent a hydrogen atom or an aliphatic radical, with the further limitation that at least one of R_6 or R_7 must be different from hydrogen and the other must contain between 10 and 22 carbon atoms. So, on the one hand the claims state that one or both of R_6 and R_7 may be hydrogen, and on the other hand the claims require that neither R_6 nor R_7 can be hydrogen.

Claims 2-10 are indefinite because although they are drawn to subgenuses of claim 1, they fail to begin with a definite article. Because these claims do not begin with a definite article, one cannot know which compositions embraced by claim 1 are also embraced by these claims. Use of a definite article would make it clear that the dependent claims embrace all of the compounds of claim 1, except as further and clearly limited.

Claim 2 is indefinite because it is ambiguous due to the use of the conjunction "and" immediately after the phrase "on the one hand". The claim should be redrafted to require that "the group R1 is bonded to either one of Z or

V, or alternatively is bonded to REP via Y. Deletion of jargon such as "on the one hand" and "on the other hand" is suggested in the interest of clarity.

Claim 3 is indefinite because it is unclear what is, and is not, a "member". Does this term exclude hydrogen atoms?

Claim 4 is indefinite because it is unclear whether or not the limitations regarding R_3, R_4, and R_5 are meant to be applied to each group (NR_4-$(CHR_3)_r$) or only to one or several such groups.

Claims 6 and 7 are indefinite because they recite "the groups R_6 and R_7" without proper antecedent basis.

Claim 11 is indefinite because it recites "the analogous lipopolyamines" and "the cyclization" without antecedent basis.

Claims 13-23 are indefinite because although they are drawn to subgenuses of claim 12, they fail to begin with a definite article. Because these claims do not begin with a definite article, one cannot know which compositions embraced by claim 12 are also embraced by these claims. Use of a definite article would make it clear that the dependent claims embrace all of the compositions of claim 12, except as further and clearly limited.

Regarding claim 16, the phrase "such as in particular" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 17 and 18 are indefinite because they recite "the nucleic acid" without proper antecedent basis. These claims depend from claim 14 which depends from

either one of claims 12 or 13. To the extent that claims 17 and 18 depend from claim 12 and not claim 13, they lack antecedent basis for "the nucleic acid", because claim 12 recites no antecedent for a nucleic acid.

Claim 18 is indefinite because it is unclear what are the metes and bounds of "derivatives". Neither the claim nor the specification defines the term in this context, so one of skill in the art cannot know what are the metes and bounds of the claim. This claim is also indefinite because it is unclear if the number of peptide units is limited or not. First, the claim states that it is "possible for the number of units to vary between 2 and 10". It is not clear if it is also possible, or not, for the number of units to vary otherwise. Second, the claim states that the number of units may be repeated continuously or otherwise. It is unclear if this repetition is limited to a total of 10 units, i.e. two units could be repeated as many as 5 times, or if there is no limit on the number of repetitions.

Claims 24 and 25 provide for the use of a compound, but, since the claims do not set forth any steps involved in the methods/processes, it is unclear what methods/processes applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 27 is indefinite because although it is drawn to subgenuses of claim 26, it fails to begin with a definite article. Because this claim does not begin with a definite article, one cannot know which methods embraced by claim 26 are also embraced by

claim 27. Use of a definite article would make it clear that claim 27 embraces all of the methods of claim 12, except as further and clearly limited.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 25, 28, and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 28 is directed to a method of treating diseases by administering a compound of formula I combined with a nucleic acid encoding a protein, or with a nucleic acid that can be transcribed into a nucleic acid capable of correcting said diseases. Claim 29 is directed to a method of treating a disease by administering to cells by an intramuscular route a nucleolipid complex comprising a compound of one of claims 1-9 and a nucleic acid. Claims 24 and 25 are directed to uses of a compound for making a medicament for treating diseases by transfer of nucleic acids into cells.

In view of the specification at page 1, lines 4-10, the compounds of formula 1 are intended to be cationic lipids. In the view of the specification at page 23, lines 10-16, the scope of nucleic acids contemplated includes those encoding therapeutic

polypeptides and therapeutic antisense molecules. The claims do not limit the scope of diseases which may be treated by the claimed method. The specification at pages 25 and 26, considers a wide variety of gene to be therapeutic, including for example, dystrophin, and the CFTR protein associated with cystic fibrosis. As such, the claims embrace methods of treating any disease, including cystic fibrosis and muscular dystrophy, and one must consider several facets of the invention including:

-the general state of the art of gene therapy,

-the general state of antisense therapy

-the state of the art of treating diseases using genes suggested in the specification, such as dystrophin and CFTR genes, and

-the use of cationic lipids in gene therapy.

While the specification provides sufficient guidance reasonably enable the use of cationic lipids for delivery of DNA to cells, claims limited specifically to generic gene therapy methods of treating a wide variety of diseases, including e.g. cystic fibrosis and muscular dystrophy, the specification provides insufficient guidance to overcome the unpredictability in the art of treating diseases by gene therapy, as discussed more fully below.

Gene therapy in general at the time of the invention

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by reviews at the time of the invention. Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col

1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (Stem Cells 18: 19-39, 2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (Nature Review, Genetics 1: 91-99, 2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph. Thus those of the highest skill in the art before, at, and after the time of the invention, felt that the general art of gene therapy was highly unpredictable and could not be practiced with routine success. Indeed at the time of the invention there was no report of successful gene therapy in humans.

Use of cationic lipids in gene therapy

Cationic lipids are non-viral delivery vectors that are being developed to circumvent some of the art recognized problems with viruses, primarily those pertaining

to safety. Cationic lipid vehicles offer the advantages of ease of preparation, no replication risk, and generally lower risk of immune responses. However, a review of the prior art and the art subsequent to filing shows that cationic lipids offer poorer efficiency of gene delivery and expression than do the viral vectors that have proved inadequate for the purpose of gene therapy. See e.g. Ross et al (Human Gene Therapy 7: 1781-1790, 1996), Table 2 at page 1783, and first full paragraph of column 2 on page 1783. Nishikawa et al (Human Gene Therapy 12: 861-870, 2001) taught that factors contributing to the poorer efficiency of cationic nonviral gene delivery include attraction of serum proteins and blood cells, and the difficulty in achieving target-specific gene transfer. See abstract, page 861, column 1, lines 9-17, page 862, column 1, lines 7-9, page 864, column 2, second full paragraph. Additional problems include recognition of unmethylated CpG dinucleotides in expression vectors comprising bacterial DNA sequences (see page 865, paragraph bridging columns 1 and 2), release from endosomes prior to lysosomal degradation, poor stability of DNA in the cytoplasm, and the inhibitory effects of cationic lipids in the nucleus (see 866, column1 to end.) Romano (2000) also considered the advantages and disadvantages of cationic lipids as delivery vehicles and noted that they did not allow specific targeting, had low transfection efficiency, gave only transient expression, were difficult to use in vivo, and could give rise to immune responses. See Table 1, on page 23, and first full paragraph of column 2 on page 30. As late as 2003, those of skill in the art still concluded that cationic lipids "are currently not efficient enough to be clinically viable" (Miller (Curr. Med. Chem. 10)14): 1195-1211, 2003)), see abstract, and "are still far from being

viable alternatives to the use of viral vectors in gene therapy" (Pedroso de Lima et al (Curr. Med. Chem. 10)14): 1212-1231, 2003)).

Gene therapy of Muscular Dystrophy

The state of the art of gene therapy of DMD is set forth by Karpati and Acsadi (Clin. Invest. Med. 17(5): 499-509, 1994) who teach that several unanswered questions remain to be addressed prior to development of gene therapy for DMD including determining the structure of the dystrophin cDNA to introduce; what type of promoter to use; the method of gene targeting; the required duration of gene expression; and the appropriate route of delivery. See Table 3 at page 501, column 2. Pertinent to the issues of delivery, targeting, and expression, the authors point out that because of the multinucleate nature of muscle cells, and because dystrophin is deposited near the nucleus where its message was expressed, the majority of myonuclei should acquire a normal allele if most of the muscle fiber is to be covered by dystrophin. However, because muscle fibers are surrounded by a well-developed extracellular matrix, efficient gene delivery is problematic. See page 501, column 1, lines 5-12 and 30-32. With respect to gene delivery systems, the authors teach that a variety of techniques including cationic liposomes have not produced acceptable results *in vivo*. See page 502, column 2, items a-c. Karpati and Acsadi also discuss problems associated with expression of delivered genes, citing degradation of the delivered nucleic acid, promoter silencing, mRNA instability, or destruction of the transfected cell by host immune response. See page 504, paragraph bridging columns 1 and 2. Thus, those of the highest level of skill in the art of therapeutic use of dystrophin at the time the invention

was essentially echoed the concerns of Verma, Anderson, Somia, and Romano, above regarding the unpredictable nature of gene therapy and the technical difficulties regarding delivery and expression of therapeutic genes.

Gene therapy of Cystic Fibrosis

The state of the art of CF gene therapy at the time of the invention is set forth by several authors. The example of CF shows why gene therapy must be tailored to fit specific diseases on a case by case basis, and why no single delivery method or composition will be effective to treat all diseases. For example, one of the most important barriers to gene therapy of CF is the lack of information regarding the appropriate target cells for gene delivery. Rosenfeld and Collins (Chest 109:241-252, 1996) teach that it is unclear exactly which cells should receive [gene therapy]", stating that "[t]he difficulty in determining which cells to target relates to an inability to draw parallels between the normal pattern of CFTR expression and the development of CF in lung disease. In normal individuals, the surface epithelium of small airways expresses very low levels of CFTR, while the submucosal glands found exclusively in large airways express much higher levels. In contrast, in CF, the most important pathologic consequences occur first in the small airways with alveolar damage as a consequence. Little if any clinically significant disease ever occurs where the submucosal glands are found." Boucher (TIG 12(3): 81-84, 1996) notes that this issue is relevant to strategies for vector delivery because while the superficial epithelium of airways can be reached by lumenal vector delivery, the submucosal glands may require systemic administration. See page 1 of reprint, column 2, last sentence of first full paragraph. Rosenecker (Eur.

J. Med. 23(3): 149-156, 3/1998) teaches that "[t]opical administration of gene transfer vectors to airways is impeded by surface fluid, mucus plugging the airway lumen, and the ciliated apical surface of epithelial cells" and that the submucosal glands are inaccessible for topically applied formulations. Thus systemic delivery via the blood stream is indicated. See page 152, column 2, lines 1-15 of second full paragraph. Thus, at the time of the invention, those of skill in the art were uncertain as to which cells should be considered targets for CF gene therapy, and what route of delivery would lead to success, assuming the art-recognized problems relating to gene expression after delivery could be solved.

The situation in CF gene therapy is further complicated by an incomplete understanding of the pathophysiology of the disease. Briefly, the molecular problem responsible for CF is a defect in a chloride ion transporter known as CFTR. One hypothetical explanation for the progress of the disease depends on a failure to transport chloride ions, leading to abnormal absorption of sodium ions by the epithelium. This leads to dehydration and thickening of the mucus in the lungs, which in turn leads to a variety of pathophysiological outcomes including inflammation, repeated infections, and decreasing pulmonary function. Alternatively, the defect in CFTR could somehow affect the actual composition of mucus in the lung, resulting in the recognized pathologies. See Wilson (1995) paragraph bridging pages 2547 and 2548. Thus a primary focus of treatment is the restoration of chloride ion transport. Boucher (1999) teaches that it is likely that the percentage of epithelial cells requiring functional correction to restore normal chloride ion transfer *in vivo* may well exceed 10%, and

advises that the simplest strategy to assure efficacy is to mimic the normal pattern of *in vivo* expression by achieving gene expression in 100% of lung epithelial cells. See paragraph bridging pages 441 and 442, page 442 column 1, lines 25-30, and 42- 45. Boucher concludes that a one or two order of magnitude increase in *in vivo* gene transfer efficiency, above that observed in clinical trials, will be required for therapeutic relevance in CF treatment. See page 444, column 2, first sentence of second full paragraph. The state of the art at the time of the invention provided no means to achieve this level of delivery, Verma, Anderson, Somia and Romano, above. Clinical studies have shown success in partially correcting chloride ion transport, however Alton and Geddes (1997) teach that it is unknown whether the chloride or sodium defect associated with CF is the more important error to correct, and that the degree of correction needed for clinical benefit of these defects is unknown. See page 45, lines 7-10 of first full paragraph. Furthermore, Davies (1998) teaches that if normalization of sodium ion transport is required for therapeutic effect, then the levels of gene transfer observed to date will be inadequate because correction of sodium ion transport has not been achieved in the majority of preclinical and clinical studies. See page 294, column 2, lines 22-28. Rosenfeld (1996) indicates that although restoration of chloride conductance in monolayer cells is achieved by transfection of 5-7% of the cells, normalization of sodium ion reabsorption will require transfection of a much higher percentage of cells. See page 243, column 1, lines 15-18. For all these reasons it was apparent at the time of the invention that the practice of gene therapy of CF was highly unpredictable, and that the state of the art could not support gene therapy of CF.

Shortly after the application was filed, Boucher (1999) summarized the state of the art by stating that "despite an impressive amount of research in this area, there is little evidence to suggest that an effective gene transfer approach for the treatment of CF lung disease is imminent."

Antisense gene therapy

The state of the art with respect to antisense therapies indicates a high level of unpredictability. Crook (In Basic Principles of Antisense Therapeutics, Springer-Verlag, Eds, New York, pgs. 1 and 4), teaches that although antisense techniques have progressed rapidly, "the technology remains in its infancy", and the utility of the approach is still debatable (pg. 1, Introduction). Crook points out several factors which may influence the biological effect of an antisense oligonucleotide (AODN), including the rate of uptake of the AODN, rate of distribution within the target cell, stability within the target cell, local concentration of the oligonucleotide, and the concentration and stability of the target mRNA (pgs. 1 and 4). Furthermore, Branch (Trends in Biochem. Sci 23: 45-50, 1998) teaches that selection of appropriate antisense sequences is difficult because secondary structures of mRNAs *in vivo* frequently restrict access of antisense oligonucleotides to the target sequence (page 45, col. 3. first para., page 48, last para. and page 49). Branch states, "Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49, col. 2, last para.). Ho and Parkinson (Sem. Drug Discov. 24(2): 187-202, 1997) teach that although antisense therapy is simple in theory, it "has proven to be much more complex in practice. A number of important challenges in the preclinical development of antisense

oligonucleotides have been identified, including stability, sequence length, cellular uptake, target sequence selection, appropriate negative controls, oligonucleotide: protein interactions, and cost of manufacture." The authors conclude that "[c]ontinued progress in this arena will require that many of the preclinical challenges confronting antisense development are satisfactorily resolved." See abstract. Akhtar (J. Antimicrob. Chemother. 38(2): 159-165, 1996) teaches that "a healthy degree of concern exists among scientists and administrators as to whether antisense and, to some extent, ribozyme oligonucleotides will ever become useful therapeutic agents." See page 163, column 1, lines 5-14 of first full paragraph. Thus, at the time the invention was made, there was considerable unpredictability in the design of antisense oligonucleotides, their delivery and pharmacodynamics, and most importantly, whether or not they would ultimately have any therapeutic value. The field of antisense, to date, does not provide guidelines by which antisense can be routinely delivered to generally any cell type in vivo (whole organism) at a concentration effective to result in a predictable therapeutic effect.

Against this background, the specification teaches no working examples of therapeutic delivery of any gene to any patient. Further, the specification does not provide specific guidance by which one skilled in the art would expect to be able to deliver antisense to target cells or tissue in vivo at a concentration effective to provide a pharmaceutical effect or to treat the broad range of diseases encompassed by the claims. The cationic lipids of the invention are used to deliver to mice non-therapeutic nucleic acids by intravenous and intramuscular routes, but transfection efficiency is no

better than that observed in the prior art for a cationic lipid or naked DNA, respectively. See Figures 7 and 8. For this reason, absent further guidance in the specification, one of skill in the art would not expect to improve on the results achieved in the prior art which those of skill in the art have judged to be inadequate. However, the specification provides no further guidance for any gene therapy beyond that which was available in the prior art, except for the invention of new cationic lipids. As discussed above (see Verma, Anderson, Somia, and Romano above), the art of gene therapy generally is highly unpredictable and scientifically immature, particularly as shown by the specific examples of DMD and CF gene therapy, such that enablement of gene therapies must generally be considered on a case by case basis with special attention paid to the nature of disease, the therapeutic gene, expression construct, the nature of the vector, and the mode of delivery. The instant specification does not address these issues for specific diseases.

In view of the breadth of diseases embraced by the claims, the state of the art, the unpredictability in the art as assessed by those of the highest level of skill, the lack of any working example of therapy in the specification, and the failure to provide the guidance that is lacking in the prior art, one of skill in the art could not practice the invention as intended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-29 are rejected under 35 U.S.C. 102(b) as being anticipated by either one of Byk et al. (WO 9951581, published 10/14/99) or Byk et al (FR98/04121, published 1/19/99).

These documents are the priority documents listed in the instant Declaration for Patent Application, and they provide full support for, and thereby anticipate, the instant claims to the extent that the disclosure is enabling. This rejection may be overcome by insertion in the first line of the instant specification of a statement claiming priority to these documents, provided the priority claim is made during the pendency of the application and within the time limit set forth in the PCT and Regulations of the PCT. See 37 CFR 1.55(a)(1)(ii).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax

number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.